



III. Disorders of Sexual Differentiation (DSD or Formerly Known as Ambiguous Genitalia)

A. Normal sexual differentiation (Figure 6-3)

1. During the first 7 weeks of gestation, the gonadal tissue remains undifferentiated. The final appearance of gonadal tissue is dependent on both genetic and hormonal influences.
2. Male sexual differentiation is an active process, whereas female sexual differentiation develops by default when genetic and hormonal influences are absent.

B. Male sexual differentiation is initiated by the SRY gene located on the short arm of the Y chromosome. By 9 weeks' gestation, the SRY gene differentiates the gonads into fetal testes, which subsequently produce testosterone and anti-Müllerian hormone (AMH or previously called Mullerian inhibiting substance).

1. **Internal ducts.** In the genetic XY male, testosterone made by fetal Leydig cells stimulates the development of the Wolffian ducts (epididymis, vas deferens, and seminal vesicles), and AMH made by fetal Sertoli cells inhibits the development of the Müllerian structures (fallopian tubes, uterus, and upper one-third of the vagina).
2. **External genitalia.** The conversion of testosterone to dihydrotestosterone (DHT) by 5α -reductase occurs in the skin of the external genitalia. DHT is responsible for penile enlargement, scrotal fusion, and the entire masculinization of the external genitalia. By 12 weeks, this process is complete, except for penile growth, which continues to term.

C. Female sexual differentiation. In the absence of the SRY gene, the gonads become ovaries.

1. **Internal ducts.** Because there is no testicular tissue, there is no secretion of testosterone or of AMH, resulting in the regression of the Wolffian ducts and the development of the Müllerian structures, respectively.
2. **External genitalia.** The external genitalia do not virilize because there is a lack of testosterone and of DHT. This results in the development of the labia, the clitoris, and the lower two-thirds of the vagina.

D. Differential diagnosis of the undervirilized male (i.e., a neonate who usually has a 46, XY karyotype with ambiguous genitalia and one or both testes palpable; Figure 6-4).

1. **Disorders of testosterone synthesis.** Many inherited enzyme deficiencies result in low testosterone levels (i.e., any enzyme deficiency in the pathway of androgen synthesis in Figure 6-5).
 - a. **Smith–Lemli–Opitz syndrome.** This syndrome is due to defective 3β -hydroxysteroid- $\Delta 7$ reductase, the last step in cholesterol biosynthesis. Without functional cholesterol biosynthesis, steroid hormone production is defective. Patients can have microcephaly, cleft lip/palate, liver disease, syndactyly of the second and third toes and holoprosencephaly. Genital ambiguity is variable.
 - b. **5α -Reductase deficiency.** Patients cannot convert testosterone to DHT, the more potent version of testosterone that binds to androgen receptors and virilizes the external genitalia. Patients may present with ambiguous genitalia, such as varying degrees of hypospadias, or as adolescents with incomplete pubertal progression. Some patients present as adolescent females who do not develop breast tissue (as opposed to patients with androgen insensitivity—see below). A ratio of testosterone:DHT of $>20:1$ with β -hCG stimulation strongly supports the diagnosis. By comparison, the ratio in normal male infants is typically <10 .
2. **Disorders of testosterone action are usually due to androgen insensitivity.** These patients have X-linked partial or complete peripheral androgen resistance resulting from defective androgen binding to the androgen receptor in the genital tissue. Presentation is

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Hypospadias is a birth defect in boys in which the opening of the urethra is not located at the tip of the penis. In boys with hypospadias, the urethra



highly variable. Complete forms typically present as females with primary amenorrhea and breast development, whereas partial forms may present with some degree of impaired virilization observed in the neonate (such as cryptorchidism or hypospadias). Mullerian structures are usually absent. Patients have normal adrenal metabolites (17-OHP levels, etc.), but exaggerated levels of testosterone and DHT are seen after β -hCG stimulation.

3. Disorders of gonad differentiation

- a. **Gonadal dysgenesis (GD). May be complete, partial, or mixed.** Karyotypes are diverse and may include 45, XO/46, XY mosaicism. The clinical presentation is variable, as patients may have completely normal external female genitalia, to some degree of ambiguous genitalia with some internal Mullerian structures (i.e., fallopian tubes, etc.). Typically these patients have low to undetectable levels of AMH, and the gonads do not respond to stimulation with β -hCG.
- b. **True hermaphroditism (also known as ovotesticular DSD).** These patients may have ambiguous genitalia with both ovarian and testicular gonadal tissue and both Mullerian and Wolffian internal ducts. The gonads generally have some function, and levels of AMH are normal. The gonads do respond to β -hCG stimulation. Usually the karyotype is 46, XX, but it can be 46, XY.

E. Differential diagnosis of ambiguous genitalia in the virilized female (i.e., a female who is a genetic XX with ambiguous genitalia and no gonads palpable; Figure 6-6).

1. **CAH caused by 21-hydroxylase (21-OH) deficiency is the most common cause of female pseudohermaphroditism** [see section IV.C]. 11 β -Hydroxylase (11 β -OH) deficiency and 3 β -hydroxysteroid dehydrogenase deficiency are other causes of CAH.
2. **Virilizing drug** used by mother during pregnancy
3. **Virilizing tumor** in mother during pregnancy

F. Evaluation of the patient with ambiguous genitalia

1. **Careful history.** Maternal history of drugs or virilization during pregnancy, family history of androgen insensitivity, CAH, or consanguinity.
2. **Physical examination.** Presence or absence of gonads, labioscrotal swelling, bifid scrotum, labial fusion, urogenital sinus, or hypospadias. Palpable gonads suggest that the neonate has an XY karyotype. (Key point: Increased blood pressure suggests CAH with 11 β -OH deficiency, and decreased blood pressure suggests adrenal insufficiency; see sections IV.B.1.a and IV.C.3.b.)
3. **Chromosome studies** (including polymerase chain reaction [PCR] or fluorescent in situ hybridization [FISH] for the SRY gene, and a karyotype)
4. **Radiographic studies** include pelvic ultrasound and genitogram to define the internal genitourinary anatomy.
5. **Laboratory studies**
 - a. **Undervirilized males.** Besides the abovementioned chromosome studies, electrolytes and 17-OHP levels should be ordered. DHT and testosterone levels (preferably after β -hCG stimulation) with LH, FSH, AMH, and androstenedione levels may be warranted. If serum testosterone is low, further evaluation for an inborn error in androgen synthesis is indicated.
 - b. **Virilized females.** Serum electrolytes, testosterone level, and further studies to look for evidence of CAH (17-OHP, etc.) are indicated [see Figure 6-5 and section IV.C.4].
6. **Management.** Evaluation is complex, and gender assignment should not be rushed. Generally, these patients should be referred to centers with multidisciplinary teams of pediatric endocrinologists, geneticists, and pediatric urologists. The initial focus should be on clear communication with the family regarding the process of evaluation.

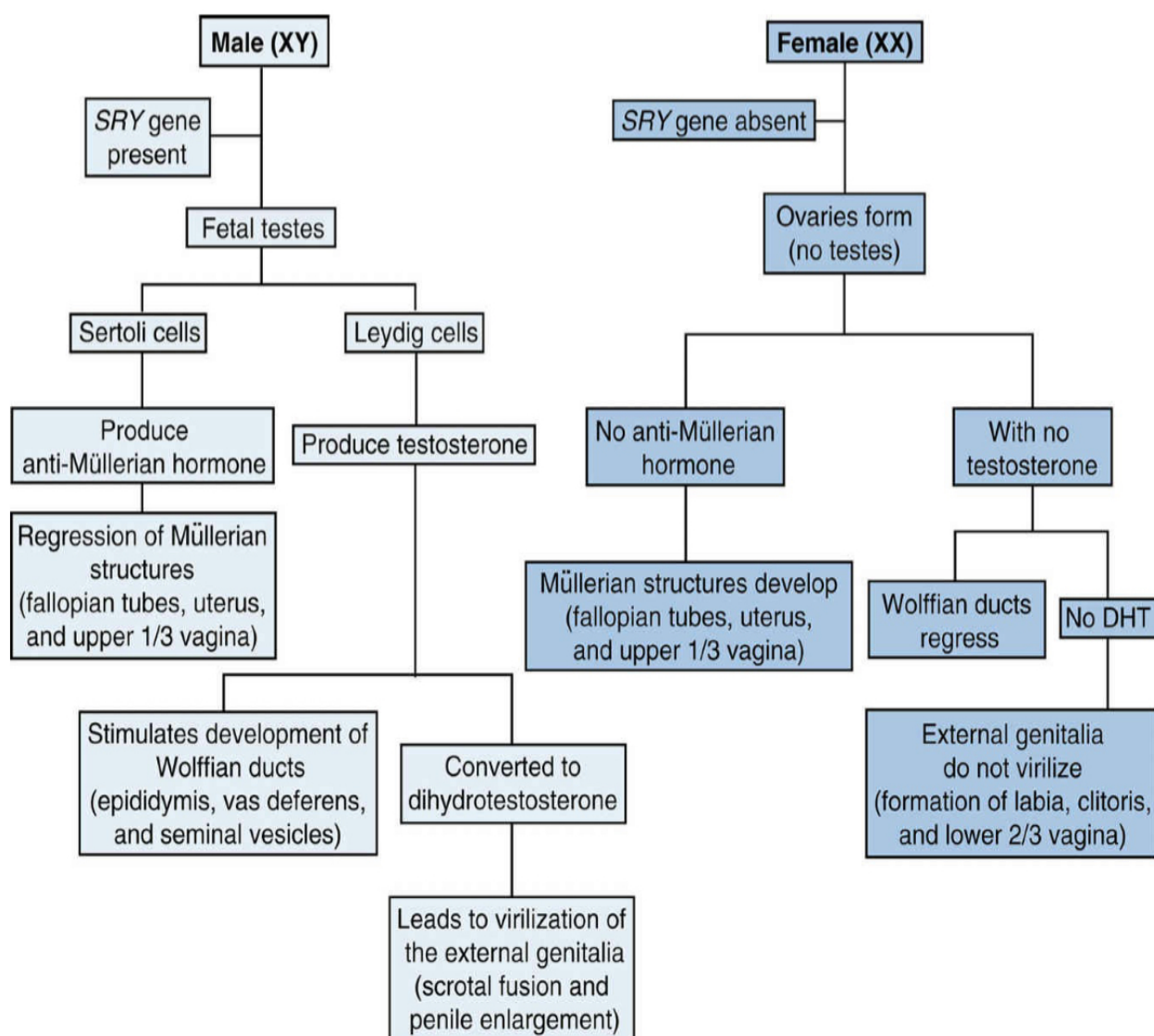


FIGURE 6.3 Normal sexual differentiation in utero. DHT = dihydrotestosterone.

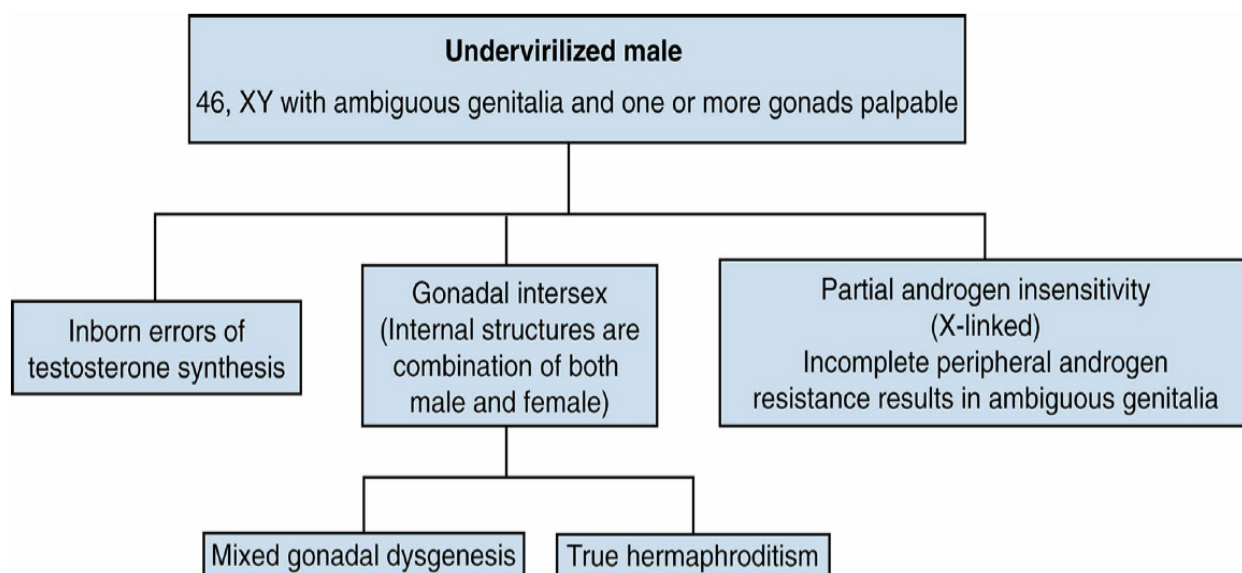


FIGURE 6.4 Differential diagnosis of ambiguous genitalia in an undervirilized male.